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A Novel Isoform of Platelet Glycoprotein Ibα Is Prevalent in African Americans

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The heavy chain of platelet glycoprotein Ib (GPIb) contains two prevalent sequence polymorphisms. The first, Thr/Met^{145} is responsible for the human platelet alloantigen system, human platelet antigen (HPA)-2. The second is a tandem repeat polymorphism that consists of four variants, A, B, C, and D. Previous linkage studies in Caucasian and Eastern Asian populations have demonstrated that HPA-2a (Thr^{145}) is associated with variants C and D, while HPA-2b (Met^{145}) is associated with variants A and B. We have determined HPA-2 and variable number of tandem repeats (VNTR) genotypes in three different North American ethnic groups. The gene frequency of HPA-2b in the North American Indians was intermediate between African Americans and Caucasians, and similar to the frequency previously reported in Japanese. Furthermore, the VNTR-A allele, which previously has been reported only in Eastern Asian populations, was present in two of 101 North American Indian individuals. These data are consistent with the hypothesis that the first Native Americans migrated to North America from Eastern Asia. Analysis of HPA-2 and VNTR haplotypes demonstrated an unexpected linkage pattern in the African American population. A rare GPIbα isoform, HPA-2b/VNTR-C, was present in 2.2% of African American haplotypes. Furthermore, a novel GPIbα isoform, HPA-2a/VNTR-B, was present in 6.5% of African American haplotypes. These data suggest a more complex evolutionary pattern of GPIbα isoforms than previously proposed. Am. J. Hematol. 60:77–79, 1999.

Key words: glycoprotein Ib; platelet antigen; VNTR; HPA-2; polymorphism

INTRODUCTION

Platelet membrane glycoprotein Ib (GPIb) is composed of two polypeptide chains, α (150 kD) and β (27 kD), linked by disulfide bonds. Two polymorphisms within the GPIbα chain that affect the amino acid sequence have been described. The first, human platelet antigen (HPA)-2, is due to a single base change that results in a Thr(ACG)/Met(ATG) substitution at amino acid 145 [1,2]. The second polymorphism results from a variable number of tandem repeats (VNTR) of a 13 amino acid sequence (Ser^{399} to Thr^{411}) that is present in either one, two, three, or four copies (variants, D, C, B, or A) [3].

The distribution of the GPIbα VNTR and HPA-2 alleles varies considerably among different populations. For example, the VNTR-A allele is found almost exclusively in Eastern Asia [4,5]. In addition, linkage disequilibrium between GPIbα VNTR and HPA-2 has been reported: variants A and B are linked to the HPA-2b (Met^{145}) allele, while variants C and D are linked to the HPA-2a (Thr^{145}) allele [4–6]. In this study, HPA-2 and VNTR genotypes were determined in three different North American ethnic groups.

MATERIALS AND METHODS

After obtaining informed, written consent, EDTA-anticoagulated peripheral blood samples were obtained from healthy, unrelated donors residing in the Pacific Northwest. These included 125 Caucasians, 121 African Americans, and 101 North American Indians.

Genomic DNA was purified using the Puregene Iso-

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TABLE I. Calculated GPIbα Gene Frequencies of HPA-2 (Thr/Met^{145}) and VNTR Alleles in Three North American Populations*

	American Caucasians (N = 125)	African Americans (N = 121)	American Indians (N = 101)
HPA-2a (Thr^{145})	0.924	0.822	0.881
HPA-2b (Met^{145})	0.076	0.178	0.119
VNTR-A	—	—	0.010
VNTR-B	0.076	0.211	0.104
VNTR-C	0.840	0.752	0.797
VNTR-D	0.084	0.037	0.089

*GPIbα, platelet membrane glycoprotein Ib alpha; HPA, human platelet antigen; VNTR, variable number of tandem repeats.

TABLE II. Association Between GPIbα VNTR and HPA-2 Genotypes in Three North American Populations*

		VNTR Genotype[a]								
		AC	AD	BB	BC	BD	CC	CD	DD	Total
American Caucasians (N = 125)	HPA-2 (aa)	0	0	0	0	0	89	19	1	109 (87.2)
	HPA-2 (ab)	0	0	0	13	0	0	0	0	13 (10.4)
	HPA-2 (bb)	0	0	3	0	0	0	0	0	3 (2.4)
	Total (%)	0 (0.0)	0 (0.0)	3 (2.4)	13 (10.4)	0 (0.0)	89 (71.2)	19 (15.2)	1 (0.8)	125
African Americans (N = 121)	HPA-2 (aa)	0	0	0	10	1	65	7	0	83 (68.6)
	HPA-2 (ab)	0	0	1	27	1	4	0	0	33 (27.3)
	HPA-2 (bb)	0	0	5	0	0	0	0	0	5 (4.1)
	Total (%)	0 (0.0)	0 (0.0)	6 (5.0)	37 (30.6)	2 (1.7)	69 (57.0)	7 (5.8)	0 (0.0)	121
American Indians (N = 101)	HPA-2 (aa)	0	0	0	0	0	64	13	1	78 (77.2)
	HPA-2 (ab)	1	1	0	17	2	1	0	0	22 (21.8)
	HPA-2 (bb)	0	0	1	0	0	0	0	0	1 (1.0)
	Total (%)	1 (1.0)	1 (1.0)	1 (1.0)	17 (16.8)	2 (2.0)	65 (64.4)	13 (12.9)	1 (1.0)	101

*GPIbα, platelet membrane glycoprotein Ib alpha; VNTR, variable number of tandem repeats; HPA, human platelet antigen.
[a]Numbers in parentheses indicate percent of total.

lation Kit (Gentra Systems Inc., Research Triangle Park, NC), according to the manufacturer's instructions. Genotyping for the HPA-2 [6] and VNTR [4] polymorphisms was performed according to previously published methods.

RESULTS AND DISCUSSION

HPA-2 and VNTR Allele Frequencies

The HPA-2 and VNTR calculated gene frequencies for the three ethnic groups are shown in Table I. The gene frequency of the HPA-2b allele was highest in African Americans and lowest in Caucasians, as reported by others [6,7]. The intermediate HPA-2b frequency in our North American Indian population (0.119) is similar to the frequency reported in Japan (0.136) [8]. Furthermore, the VNTR-A allele, which previously has been reported only in Eastern Asian populations [3–6], was present in two of 101 North American Indian individuals. These data are consistent with the hypothesis that the first Native Americans migrated to North America from Eastern Asia. Curiously, the North American Indian HPA-2b gene frequency differs from that recently reported in a population of South American Indians from the Brazilian Amazon (0.04) [9]. This may represent genetic drift following migration of Native Americans from North to South America. Alternatively, the Brazilian American Indians may have descended from another population such as the Polynesians [10].

Association Between HPA-2 and VNTR Genotypes

The association between HPA-2 and VNTR genotypes in our three populations is shown in Table II. Analysis of genetically informative Caucasian individuals (i.e., homozygous for one or both polymorphisms) confirmed the previously reported linkage disequilibrium: HPA-2b is associated with variant B (or variant A in Asians), while HPA-2a is associated with variants C or D [4–6]. This same linkage pattern was present in the North American Indians, except for one individual who had the haplotype HPA-2b/VNTR-C. This rare haplotype has been previously reported in a single Caucasian family [6].

Unexpectedly, a somewhat different linkage pattern

was present in our African American population. Analysis of the 93 informative donors indicates that the rare HPA-2b/VNTR-C isoform is present in 4 of 186 (2.2%) haplotypes. Thus, the HPA-2b/VNTR-C haplotype appears to be considerably more common in African Americans than any other ethnic group analysed to date. Even more remarkably, in 12 of the 93 (12.9%) genetically informative African Americans, the HPA-2a allele was associated with the VNTR-B allele. This HPA-2a/VNTR-B haplotype is therefore present in 12 of 186 (6.5%) African American haplotypes, and heretofore has not been described in any other population.

An evolutionary model of GPIbα isoforms has been proposed which includes: 1. a linear, step-wise addition of the 39 bp tandem repeat sequence to the ''ancestral'' HPA-2a/VNTR-D variant, and 2. the occurrence of the Thr^{145} to Met^{145} substitution around the time that a tandem repeat was added to variant C to form variant B [5,6]. Our finding of the new HPA-2a/VNTR-B isoform suggests a more complex evolutionary model in which the triplicated repeat also occurred *prior to* the Thr/Met^{145} substitution. This event may have occurred relatively recently in human evolution, possibly as a result of a founder effect in African Americans. Confirmation of this hypothesis awaits analysis of GPIbα alleles in other African and non-African populations. From a platelet function standpoint, in vitro differences in thrombogenicity have yet to be demonstrated between HPA-2 and VNTR alleles. However, the recent report of HPA-2b and VNTR-B alleles as prothrombotic risk factors for cardiovascular disease [11] suggest that these variants may have evolved at least in part because of selective pressure to promote hemostasis.

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